

Application No.: 09/733,773

Attorney Docket No.: SALK2410

Filing Date: December 8, 2000

(088802-5651)

Response to Office Action (mailed December 23, 2003) faxed May 24, 2004

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**Remarks**

Courtesies extended to Applicants' representative in the personal interview held on February 4, 2004, are acknowledged with appreciation.

In accordance with the present invention, there are provided the crystal structure and atomic coordinates of a WW domain co-complexed with a WW domain binding agent. The invention provides methods of identifying WW domain binding agents employing such crystal structure and atomic coordinates. The invention further provides computer programs for use in developing WW domain binding agents.

Claims 1-28 were pending prior to the present communication. Claims 17-28 were previously withdrawn by the Examiner pursuant to Applicants' provisional election of Group I (*i.e.*, claims 1-16). Claims 17 and 18 have been rejoined with the Group I claims by the Examiner pursuant to Applicants' Response filed October 1, 2003.

Claims 1, 9 and 18 have been amended herein to define Applicants' invention with greater particularity. These amendments add no new matter as they are fully supported by the specification and original claims. In addition, claims 13-17 have been cancelled herein without prejudice. Accordingly, claims 1-12 and 18 are currently under consideration. The present status of all claims in the application is provided in the listing of claims presented herein beginning on page 2.

The objection to claims 13-16 under 37 C.F.R. § 1.75, as allegedly being substantial duplicates of claim 1, is respectfully traversed. As discussed at the personal interview, claims 13-16 are alternative methods of identifying WW domain binding agents. Each of claims 13-16 require different steps, wherein certain pre-conditions must be met for individual steps. For example, claim 13 requires that the ability of a potential binding agent to compete with a WW domain substrate be determined by contacting the potential binding agent with the WW domain in the presence of a WW domain substrate. In contrast, claim 1 does not contain the same pre-condition to be met in step (d), *i.e.*, the "determining" step does not require contacting the

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potential binding agent with the WW domain in the presence of a WW domain substrate. Thus, claims 13-16 do not contain the same requirements as the steps recited in claim 1.

However, in order to advance prosecution and reduce the issues, claims 13-16 have been cancelled herein without prejudice. Accordingly, this objection to claims 13-16 under 37 C.F.R. § 1.75 is rendered moot.

The objection to claim 18 under 37 C.F.R. § 1.75, as allegedly being a substantial duplicate of claim 17, is respectfully traversed. Claim 18 requires different steps, wherein certain pre-conditions must be met for individual steps. For example, claim 18 requires that a potential binding agent be modeled using a plurality of atomic coordinates. In contrast, claim 17 does not contain the same pre-condition to be met, *i.e.*, the potential binding agent may be otherwise modeled, *e.g.*, in addition to using the atomic coordinates. Thus, claims 17 and 18 do not contain the same requirements in each step.

However, in order to advance prosecution and reduce the issues, claim 17 has been cancelled herein without prejudice. Accordingly, this objection to claim 18 under 37 C.F.R. § 1.75 is rendered moot.

The rejection of claims 1-18 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention, is respectfully traversed. Applicants respectfully submit that the claims are clear to one of skill in the art as originally presented. However, in efforts to advance prosecution and reduce the issues, claims 1 and 18 have been amended herein to define the claimed subject matter with even greater particularity.

For example, claim 1 has been amended to confirm that the claimed method combines both a virtual method and a physical method. Specifically, a potential binding agent is modeled on a computer to fit spatially into a WW domain interaction site using a plurality of atomic coordinates (see specification for support, for example, at page 42, line 5, through page 44, line 8). The ability of the potential binding agent to compete with a known WW domain substrate for

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binding to a WW domain is determined by contacting the agent with the WW domain in the presence of the known WW domain substrate (see specification for support, for example, at page 41, lines 23-29).

With respect to the use of the phrase "defined by" in claim 1, claim 1 has been amended to illustrate that a potential binding agent is modeled on a computer using a plurality of atomic coordinates obtained from a WW domain crystallized in co-complex with a known WW domain binding agent, substrate, or inhibitor. Upon computer modeling using such atomic coordinates of a protein, Applicants respectfully submit that the interaction site of a potential binding agent with the protein becomes apparent to one of skill in the art (see, for example, specification at page 42, lines 5-11; and Figure 2). First, the interaction site of a co-complexed WW domain binding agent, substrate, or inhibitor with the WW domain is readily determined using such computer modeling. Second, the potential binding agent is then modeled to "fit" into the interaction site, for example, by comparing molecular interactions and conformations (see specification for support, for example, at page 41, lines 3-18). Accordingly, one of skill in the art would readily understand the use of the atomic coordinates to model the interaction of a potential binding agent with the WW domain interaction site as determined by modeling the crystal structure.

With respect to the use of the term "WW domain", Applicants respectfully submit that the term WW domain was well-known in the art at the time of filing of the present application. For example, the specification provides exemplary groups of classes of WW domains known in the art, of which the Pin1 WW domain is an exemplary member (see specification at page 5, lines 1-15). Furthermore, the atomic coordinates of the Pin1 WW domain provided in Table 1 of the present application provide a useful way to solve the structure of other crystal forms of WW domains (see specification at page 13, lines 7-13). Accordingly, one of skill in the art would readily understand the term WW domain as used herein.

In addition, claim 9 has been amended to confirm that the method therein employs additional active steps as compared to claim 1.

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Therefore, the amended claims particularly point out and distinctly claim the subject matter of the present invention. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-18 under 35 U.S.C. § 112, second paragraph.

The rejection of claims 1-6, 8, 9 and 11-18 under 35 U.S.C. § 103(a), as allegedly being unpatentable over Ranganathan *et al.*, Cell 89:875-886, 1997 (hereinafter referred to as "Ranganathan *et al.*"), in view of U.S. Patent No. 6,495,376 issued to Lu *et al.* (hereinafter referred to as "Lu *et al.*"), is respectfully traversed. Applicants respectfully submit that none of these references, either taken alone or in combination, teaches or suggests the methods of the present invention. As acknowledged by the Examiner, "Ranganathan *et al.* do not disclose contacting binding agents and determining the ability of the agent to bind" (see Office Action, at pages 5, lines 18-20).

Thus, invention methods, as defined, for example, by claim 1, distinguish over Ranganathan *et al.* by requiring contacting the potential binding agent with a WW domain in the presence of a WW domain substrate. Moreover, Applicants' invention further distinguishes over Ranganathan *et al.* by specifically using a plurality of atomic coordinates obtained from a WW domain crystallized in co-complex with a known WW domain binding agent, substrate, or inhibitor to model a potential binding agent. In contrast, Ranganathan *et al.* study the structure of Pin1 to determine its functional properties (*i.e.*, the catalytic mechanism of its peptidyl-prolyl cis-trans isomerase activity).

Lu *et al.* is unable to overcome the deficiencies of the primary reference, because Lu *et al.* does not teach or suggest the claimed methods. The present invention, as defined by claim 1, distinguishes over Lu *et al.* by requiring the computer modeling of a potential binding agent based on atomic coordinates obtained from crystals of a WW domain. Applicants' method relies on binding agents whose three-dimensional structures indicate they are likely to have robust interactions with a WW domain. In contrast, Lu *et al.* merely discloses the interaction of WW domain-containing polypeptides with ligands using only traditional binding assays (for example, incubating an uncharacterized test compound with a WW domain polypeptide).

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Moreover, Lu *et al.* does not disclose either contacting a potential binding agent identified by modeling of atomic coordinates with a WW domain, or the determination or use of atomic coordinates obtained from a WW domain crystallized in co-complex with a known WW domain binding agent, substrate, or inhibitor.

Furthermore, there is no motivation to use the functional studies provided in Ranganathan *et al.* to model potential WW domain binding agents. The Examiner quotes Ranganathan *et al.*, which states "[s]tructural studies of Pin1 complexes **with native substrates** and systematic mutagenesis of Pin1 residues implicated in catalysis and substrate recognition should help resolve **the mechanism of Pin1-dependent cell cycle regulation**" (emphasis added, Ranganathan *et al.*, at page 884), as motivation for the methods of the present invention. Clearly, the use of native substrates in mechanistic studies cannot suggest the computer modeling of unknown potential binding agents to identify WW domain binding agents.

Therefore, neither of the cited references (Ranganathan *et al.* and Lu *et al.*), either taken alone or in combination, teaches or suggests the claimed methods. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection of claims 1-6, 8, 9 and 11-18 under 35 U.S.C. § 103(a).

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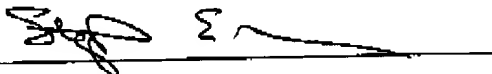
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**Conclusion**

In view of the above amendments and remarks, prompt and favorable action on all claims is respectfully requested. In the event any matters remain to be resolved in view of this communication, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

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Stephen E. Reiter  
Registration No. 31,192  
Telephone: (858) 847-6711  
Facsimile: (858) 792-6773

FOLEY & LARDNER LLP  
Customer No. 30542  
P.O. Box 80278  
San Diego, CA 92138-0278